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UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE BOARD OF PATENT APPEALS
AND INTERFERENCES

Ex parte LANFRANCO CALLEGARO, LUIGI AMBROSIO,
and ANNACLAUDIA ESPOSITO

Appeal 2011-001825
Application 09/743,333
Technology Center 1600

Before TONI R. SCHEINER, DONALD E. ADAMS and
JEFFREY N. FREDMAN, *Administrative Patent Judges*.

SCHEINER, *Administrative Patent Judge*.

DECISION ON APPEAL

This is an appeal under 35 U.S.C. § 134 from the rejection of claims 25-32 and 34-51, all the claims pending, on the grounds of obviousness and lack of written descriptive support. We have jurisdiction under 35 U.S.C. § 6(b).

STATEMENT OF THE CASE

"The present invention concerns the use of hyaluronic acid or the derivatives thereof for the preparation of a composition to treat ulcers, lesions and diverticula of the digestive and gastrointestinal apparatus" (Spec. 1: 5-8). Claim 25 is representative of the claimed subject matter:

25. A process for the preparation of a biological material for the treatment of ulcers, lesions and diverticula of the digestive and gastrointestinal apparatus, which comprises seeding and growing enterocytes optionally together with fibroblasts, mesenchymal cells, mature cells and/or epithelial cells on a bidimensional perforated membrane or on a bidimensional continuous membrane consisting essentially of at least one hyaluronic acid or a derivative thereof thereby obtaining morphologically differentiated enterocytes as confirmed by the presence of microvilli.

The Examiner rejected claims 25-32 and 34-51 under 35 U.S.C. § 103(a) as unpatentable over Valentini (US 5,939,323, August 17, 1999);

claims 25-32 and 34-51 under 35 U.S.C. § 103(a) as unpatentable over Dorigatti (WO 94/17837, August 18, 1994) and Valentini;

claims 25-32 and 34-51 under 35 U.S.C. § 103(a) as unpatentable over Soranzo (WO 96/33750, October 31, 1996) and Valentini; and

claims 25-32 and 34-51 under 35 U.S.C. § 112, first paragraph, as failing to comply with the written description requirement.

We vacate the rejections of claims 25-32 and 34-51 as unpatentable over Valentini alone, and over Dorigatti and Valentini; affirm the rejection of the claims as unpatentable over Soranzo and Valentini; affirm the rejection of claims 25-32 and 34-51 for lack of written descriptive support under 35 U.S.C. § 112, first paragraph; and enter a new ground of rejection against claims 25-32 and 34-51 under 35 U.S.C. § 112, second paragraph.

OBVIOUSNESS

The Examiner rejected all of the pending claims as unpatentable over Valentini alone; over Dorigatti and Valentini; and finally, over Soranzo and Valentini. We select claim 25 as representative of all the claims on appeal, as Appellants have not presented separate arguments for any of the claims. 37 C.F.R. § 41.37 (c)(1)(vii).

The meaning of the term "bidimensional" in the claims is central to our evaluation of the relevance of the prior art cited by the Examiner.

Findings of Fact

1. The Specification states that a "[b]idimensional or three dimensional matrix containing a hyaluronic acid derivative, may be used as support for cellular growth for the preparation of biological material containing suitable cell cultures for regenerating the walls . . . in the digestive apparatus" (Spec. 5: 23-26).

2. The Specification doesn't define the term "bidimensional," but does indicate that Laserskin® is a bidimensional matrix, while Hyaff11 3D is a three dimensional matrix (Spec. 3: 25-28).

3. According to technical information appended to the Declaration of Anna Zanellato (initially submitted May 12, 2008 ("Dec'l 1")), Laserskin® is a perforated membrane made of HYAFF11, with a thickness of 20 µm (Dec'l 1, Annex 5), while a HYAFF®11 sponge has a thickness of 4 ± 1 mm (Dec'l 1, Annex 3). It is not clear whether the HYAFF®11 sponge described in the Declaration is the same as the Hyaff11 3D or "the scaffold (in the form of a non-woven fabric)" used in the Example in the Specification (Spec. 6: 4; 7: 7, 11-12). In any case, the Specification does not disclose the thickness of Hyaff11 3D and/or the non-woven fabric.

4. According to the Specification, Caco-2 cells (derived from a human colon carcinoma) grown on Laserskin® "showed marked differentiation due to the appearance of numerous microvilli on their surfaces," while Caco-2 cells grown on "the scaffold (in the form of a non-woven fabric) and Chronoflex [polycarbonate membrane] do not show any formation of microvilli" (Spec. 7: 5-13). In addition, according to the second Declaration of Anna Zanellato (submitted April 1, 2009 ("Dec'l 2")), when Caco-2 cells "were seeded onto supports made of the total benzyl ester of hyaluronic acid" in the form of "a bidimensional continuous membrane," "a bidimensional perforated membrane (Laserskin®)," and "a non-woven 3-D matrix" (Dec'l 2, p. 2), "the bidimensional continuous and perforated membranes show[ed] an unexpectedly great improvement in ALP activity with respect to the 3-D non-woven matrix, even when the same raw material [HYAFF11] is used" (*id.* at p. 3). According to Declarant Zanellato, increased ALP activity, or "alkaline phosphates" [sic, alkaline phosphatase?] activity, "is a known Enterocyte Differentiation Marker" (*id.* at p. 2).

5. Claim 25 is directed, in relevant part, to a method comprising growing enterocytes on a perforated or continuous bidimensional membrane consisting essentially of at least one hyaluronic acid derivative, thereby obtaining enterocytes, differentiated as confirmed by the presence of microvilli.

6. None of the claims on appeal specifically requires Laserskin® or specifies any particular thickness for the membrane.

7. Valentini discloses "derivatives of hyaluronic acid as raw material to fabricate porous, degradable scaffolds for a variety of medical

purposes, including, but not limited to, tissue repair and reconstruction and wound healing" (Valentini, col. 1, ll. 64-67).

8. Valentini's "three-dimensional biodegradable scaffolds . . . [have] interconnected pores that permit cells to grow into the scaffold, . . . penetrating the scaffold with cells, and . . . eventually replacing the scaffold with tissue" (Valentini, col. 4, ll. 30-35).

9. Valentini teaches that the scaffolds "can be fabricated to virtually any shape, size or thickness, and can be produced to various porosities and pore sizes, depending upon the application" (Valentini, col. 4, ll. 35-38).

10. Valentini's "preferred hyaluronic derivative is 100% esterified hyaluronic acid-benzyl covalent conjugates, sold under the trade name HYAFF" (Valentini, col. 5, ll. 43-45).

11. Valentini teaches that the scaffolds may be used to culture cells in vitro "with the purpose of creating tissue constructs for repairing tissues and organs in vivo . . . [and] may be used to promote tissue culture of committed cells and/or differentiation of precursor cells" (Valentini, col. 8, ll. 7-11). To that end, the scaffolds may be coated with a variety of materials, including "those that effect cell migration, cell adhesion, cell commitment, cell proliferation, cell differentiation, etc." (*id.* at col. 6, ll. 28-30).

12. Valentini teaches that the scaffolds "may be used to repair defects and damage in skin, muscle and other soft tissues such as results from trauma, burns, ulcers" when "seeded with, for example, dermal fibroblasts, [and] keratinocytes" (Valentini, col. 7, ll. 53-57). "Likewise, damage to visceral organs including liver damage, heart attack damage, and

damage resulting from intestinal cancer or intestinal ulcer may be treated with the scaffolds of the invention. In these instances, the scaffolds can be seeded with cells such as hepatocytes, cardiac muscle cells, intestinal cells, etc." (*id.* at col. 8, ll. 1-6.)

13. According to Declarant Zanellato, "[i]t is known that the intestinal epithelial tissue contains at least three type[s] of cells: (i) enterocytes able to form the intestinal villi . . . (ii) goblet cells . . . [and] (iii) endocrine cells" (Dec'l 1, p. 4).

14. Dorigatti discloses multilayer non-woven materials which "can be used, for example, as non-adhesive sanitary or surgical articles in surgery, in dermatology such as in treating skin pathologies," etc. (Dorigatti 3: 20-23), wherein "[t]he layer which is to come into contact with the skin is comprised of esters of hyaluronic acid" (*id.* at 4: 26-27). Dorigatti does not disclose seeding the multilayer materials with cells of any kind. The overall thicknesses of various examples of multilayer materials are disclosed (*see* Examples 1-7), but there is no disclosure of the thickness of the layer comprised of hyaluronic acid esters.

15. Soranzo discloses a biodegradable, artificial skin comprising "a microperforated membrane based on a hyaluronic acid derivative, on which keratinocytes have been seeded and cultured" and "an underlying non-woven tissue based on a hyaluroinic acid derivative wherein fibroblasts have been seeded and left to proliferate" (Soranzo 5: 14-18; 10: 13-15).

16. The microperforated membrane used in all of Soranzo's Examples is Laserskin® (Soranzo 10-17).

17. According to Soranzo, a satisfactory artificial skin substrate "must allow for adhesion and cell growth;" and "its ideal porosity is 50%,

which gives a large surface area for cell-polymer interactions, sufficient volume for the deposit of extracellular matrix and only slight, or no, migrational impediments during *in vitro* culture" (Soranzo 3: 3, 8-11).

Discussion

The rejection over Valentini alone:

The Examiner finds that "Valentini uses [a] 3-D scaffold, [but] Valentini also indicates that the scaffold can be fabricated to any size and shape" (Ans. 7). The Examiner concludes that it would have been obvious to seed intestinal cells on a 3-D matrix consisting essentially of a derivative of hyaluronic acid, "or any other structural matrix including a 2-D matrix" (*id.* at 8), with the reasonable expectation that the cells would grow (*id.*).

Appellants contend that their membrane is "bi-dimensional," as opposed to Valentini's scaffolds, which are always "three-dimensional" with "3-D cavities that must be present in said scaffolds" to allow ingrowth of cells seeded on the scaffolds (App. Br. 15-17). Appellants argue that the skilled person would not have believed that "he/she would succeed in growing enterocytes on a bidimensional membrane that necessarily does not have the physical property of being porous, as the third dimension is negliglible by definition, and . . . cannot provide the cavities where the ingrowth of cells could take place" (*id.* at 17).

The problem with both the Examiner's and Appellants' arguments is that the Specification does not define "bidimensional," except indirectly by reference to a single example of a bidimensional matrix, Laserskin®, which Appellants inform us is a perforated membrane, 20 µm thick (FF3). Thus, we can determine from the Specification that a bidimensional matrix has

some thickness, even if we accept, as Appellants argue (App. Br. 17), that it is negligible relative to its length and width. However, we cannot determine the point at which something ceases to be bidimensional and becomes three dimensional (or, for that matter, the point at which something is perforated but not porous). In any case, the claims are not limited to Laserskin®, nor are they limited to a matrix 20 μm thick.

Thus we cannot determine whether Valentini's three dimensional scaffolds, which "can be fabricated to virtually any shape, size or thickness, and can be produced to various porosities and pore sizes" (FF9) would have suggested scaffolds of a thickness encompassed by the term "bidimensional" in Appellants' claims.

Accordingly, we will enter a new ground of rejection below under 35 U.S.C. § 112, second paragraph, and vacate the outstanding rejection of the claims under 35 U.S.C. § 103(a) as unpatentable over Valentini, as a decision would require "considerable speculation as to the meaning of the terms employed and assumptions as to the scope of such claims," and would therefore be imprudent. *See e.g., In re Steele*, 305 F.2d 859, 862 (CCPA 1962).

The rejection over Dorigatti and Valentini:

Dorigatti adds little or nothing to the teachings of Valentini, and we are left with the same problem as with the rejection of the claims over Valentini alone. Accordingly, we also vacate the rejection of the claims as unpatentable over Dorigatti and Valentini.

The rejection over Soranzo and Valentini:

This rejection stands on a different footing, and the indefiniteness of the term "bidimensional" is not an impediment to a decision because Soranzo discloses seeding and growing keratinocytes on a substrate comprising a Laserskin® membrane (FF15, FF16), which the record shows is an example of a perforated bidimensional matrix made from HYAFF11 (FF2, FF3). Soranzo's substrate further comprises an underlying non-woven tissue also comprising a derivative of hyaluronic acid (FF16). Soranzo doesn't disclose seeding enterocytes onto the substrate. However, Valentini discloses seeding cells, including intestinal cells, on a porous three dimensional matrix made from the same derivatives of hyaluronic acid as Laserskin® (e.g., HYAFF®) (FF10, FF 12), with the aim of promoting tissue culture of committed cells and/or differentiation of precursor cells (FF11). It is known in the art that intestinal cells include enterocytes, goblet cells, and endocrine cells (FF13).

We agree with the Examiner's conclusion that it would have been obvious for one of ordinary skill in the art to seed intestinal cells, including enterocytes, onto Soranzo's substrate, specifically onto the Laserskin® membrane portion of Soranzo's substrate, with a "reasonable expectation . . . that intestinal cells seeded on the hyaluronic acid membrane of Soranzo would grow and differentiate" on Soranzo's substrate (Ans. 11), given the fact that Valentini teaches that cells, including intestinal cells (FF12), which are known to include enterocytes (FF13), can be seeded and grown on a HYAFF scaffold, which can be fabricated to virtually any shape, size or thickness (FF9). Moreover, Valentini teaches that the scaffolds may be used

as supports to promote differentiation of precursor cells, given the appropriate conditions (FF11).

Appellants contend that the bidimensional membrane of the claims "allow[s] the enterocytes to grow only bidimensionally and this is not possible with the porous 3-D scaffold of Valentini et al., wherein the cells are taught to grow within the suitable provided pores" (App. Br. 17-18). Similarly, Appellants contend that "the microperforated membrane of Soranzo et al. is not used as such, but is *always coupled* with a 3-D non-woven tissue to form the final product for be used for *external purposes*" (*id.* at 21), "all of the requirements/advantages which the final product must meet are only ascribable to the 3-D structure" (*id.*), and "*cell growth is taught to require three dimensional matrixes having a porosity of preferably 50%*" (*id.* at 20-21).

Appellants' arguments are not persuasive. Claim 25 is directed to "preparation of a biological material . . . which *comprises* seeding and growing enterocytes . . . on a bidimensional perforated membrane" (emphasis added), and therefore does not preclude coupling the bidimensional perforated membrane to an underlying matrix, as disclosed by Soranzo.

Finally, we note the Declaration of Anna Zanellato, submitted with the Appeal Brief (Dec'l 2), which Appellants contend "demonstrate[s] that the claimed combination of features is neither suggested nor motivated at all by the teaching of Valentini" (App. Br. 18). According to Declarant Zanellato, the experiments described in the Declaration show that "bidimensional continuous and perforated membranes show an unexpectedly great improvement in APL [sic] activity with respect to the 3-D non-woven

matrix, even when the same raw material is used" (Dec'l 2, p. 3, emphasis omitted) and "only bidimensional continuous and perforated membranes consisting essentially of at least one hyaluronic acid or a derivative thereof can . . . achieve morphologically differentiated enterocytes as confirmed by the presence of microvilli" (*id.*). However, the Declaration does not indicate the thickness of the 3-D non-woven matrix, and the claims on appeal are not limited to seeding enterocytes onto a membrane of any particular thickness. Moreover, the Declaration does not compare seeding enterocytes onto Laserskin® alone with seeding enterocytes onto Laserskin® coupled with an underlying non-woven matrix of the type disclosed by Soranzo.

WRITTEN DESCRIPTION

The present claims recite "seeding and growing enterocytes" on a bidimensional membrane. The Examiner rejected the claims as failing to comply with the written description requirement because "the specification as filed does not envision seeding enterocytes" (Ans. 4), but only cells that "differentiate into enterocytes" (*id.*).

The test for sufficiency of a written description is "whether the disclosure clearly 'allow[s] persons of ordinary skill in the art to recognize that [the inventor] invented what is claimed.'" *Ariad Pharms., Inc. v. Eli Lilly & Co.*, 598 F.3d 1336, 1351 (Fed. Cir. 2010) (en banc) (quoting *Vas-Cath Inc. v. Mahurkar*, 935 F.2d 1355, 1562-63 (Fed. Cir. 1991)). The disclosure must "reasonably convey[ ] to those skilled in the art that the inventor had possession of the claimed subject matter as of the filing date." *Id.* at 1351. "[A] description that merely renders the invention obvious does not satisfy the [written description] requirement." *Id.* at 1352.

Findings of Fact

18. The Specification describes seeding a scaffold with colon carcinoma cells (Caco-2 cells) "that differentiate spontaneously into enterocytes typical of the mature intestinal epithelium" (Spec. 6: 9).

19. The Caco-2 cells' "[m]orphological differentiation was assessed on the basis of the presence of microvilli on the upper surface of the cells, while the biochemical differentiation was assessed on the basis of the increase of ALP activity" (Spec. 7: 1-4).

20. According to the Specification, Caco-2 cells seeded and grown on Laserskin® showed "marked differentiation" as evidenced by increased alkaline phosphatase activity and "the appearance of numerous microvilli" (*id.* at 7: 1-13), while "cell[s] grown on the scaffold (in the form of a non-woven fabric) and Chronoflex do not show any formation of microvilli, while those grown on Chronoflex alone present extroversion indicative of cell suffering" (*id.* at 7: 11-13).

Discussion

The Specification in effect defines enterocytes as intestinal cells which exhibit microvilli on their surfaces and increased ALP activity (FF18, FF19). The Specification clearly describes *seeding* scaffolds with Caco-2 cells, which the Specification teaches are capable of differentiating into cells exhibiting microvilli and increased ALP activity - given the right conditions (FF20). The Specification also clearly describes *growing* enterocytes on the scaffolds once they've differentiated. However, on the narrow issue of whether the Specification explicitly describes *seeding* the scaffolds with enterocytes, we are compelled to agree with the Examiner that it doesn't.

Moreover, given the Specifications' emphasis on identifying scaffolds which will allow seeded colon carcinoma cells to differentiate into cells exhibiting microvilli and increased ALP activity (which Appellants inform us are indicators for enterocytes (*see e.g.*, FF4)), we agree with the Examiner that the Specification does not more generally convey the concept of seeding a scaffold with already differentiated (or committed) enterocytes. Rather, the Specification conveys the concept of seeding appropriate scaffolds with cells capable of differentiating into enterocytes, and thereafter growing and obtaining morphologically differentiated enterocytes.

The rejection of claims 25-32 and 34-51 under 35 U.S.C. § 112, first paragraph, as failing to comply with the written description requirement is affirmed.

NEW GROUND OF REJECTION

Under the provisions of 37 C.F.R. § 41.50(b), we enter the following New Ground of Rejection:

Claims 25-32 and 34-51 are rejected under 35 U.S.C. § 112, second paragraph, as indefinite.

The unqualified term "bidimensional" appears in all the claims on appeal. As discussed above, the Specification does not define the term bidimensional, except indirectly by reference to a single example of a bidimensional matrix, Laserskin®, which Appellants inform us is a perforated membrane, 20 μm thick (FF3). Thus, we can determine from the Specification that a bidimensional matrix has some thickness, even if we accept, as Appellants argue (App. Br. 17), that it is negligible relative to its length and width. However, we cannot determine the point at which something ceases to be bidimensional and becomes three dimensional.

SUMMARY

We affirm the rejection of claims 25-32 and 34-51 35 U.S.C. § 103(a) as unpatentable over Soranzo and Valentini;

vacate the rejections of claims 25-32 and 34-51 as unpatentable over Valentini alone, and over Dorigatti and Valentini; and

affirm the rejection of claims 25-32 and 34-51 for lack of written descriptive support under 35 U.S.C. § 112, first paragraph.

In addition, we newly reject claims 25-32 and 34-51 as indefinite under 35 U.S.C. § 112, second paragraph.

TIME PERIOD FOR RESPONSE

In addition to affirming the Examiner's rejection of one or more claims, this decision contains a new ground of rejection pursuant to 37 C.F.R. § 41.50(b) (effective September 13, 2004, 69 Fed. Reg. 49960 (August 12, 2004), 1286 Off. Gaz. Pat. Office 21 (September 7, 2004)). 37 C.F.R. § 41.50(b) provides "[a] new ground of rejection pursuant to this paragraph shall not be considered final for judicial review."

37 C.F.R. § 41.50(b) also provides that the Appellant, WITHIN TWO MONTHS FROM THE DATE OF THE DECISION, must exercise one of the following two options with respect to the new ground of rejection to avoid termination of the appeal as to the rejected claims:

> (1) Reopen prosecution. Submit an appropriate amendment of the claims so rejected or new evidence relating to the claims so rejected, or both, and have the matter reconsidered by the Examiner, in which event the proceeding will be remanded to the Examiner. . . .
>
> (2) Request rehearing. Request that the proceeding be reheard under § 41.52 by the Board upon the same record. . . .

Should the Appellant elect to prosecute further before the Examiner pursuant to 37 C.F.R. § 41.50(b)(1), in order to preserve the right to seek review under 35 U.S.C. §§ 141 or 145 with respect to the affirmed rejection, the effective date of the affirmance is deferred until conclusion of the prosecution before the Examiner unless, as a mere incident to the limited prosecution, the affirmed rejection is overcome.

If the Appellant elects prosecution before the Examiner and this does not result in allowance of the application, abandonment or a second appeal, this case should be returned to the Board of Patent Appeals and Interferences for final action on the affirmed rejection, including any timely request for rehearing thereof.

No time period for taking any subsequent action in connection with this appeal may be extended under 37 C.F.R. § 1.136(a).

AFFIRMED; 37 C.F.R. § 41.50(b)

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